REMARKS/ARGUMENTS

The claims are 17-22. Claim 17 has been amended by removing the optional feature of the association of insulin with excipients and introducing the same into amended claim 19. In addition, the microparticles feature of having a corrugated or raisin-like surface has been introduced. This feature finds support at page 5, second full paragraph, of the disclosure where it is stated that "The microparticles obtained according to the present patent are much more than dimpled since they are corrugated or raisin like (FIGS. 1 and 2)." Claim 17 has also been amended to introduce the feature concerning the moisture content of the microparticles in the range of 2 to 8%, as disclosed in the last sentence of the paragraph bridging pages 8-9 of the disclosure. In addition, the features concerning the process by which the microparticles are obtained have been put together for the sake of clarity.

As stated above, claim 19 has been amended to refer to the feature of the association of insulin with excipients in order to make more clear the optional character of this feature with respect to the microparticles recited in claim 17 as amended. Claim 21 has been amended to refer to the subject matter

previously presented in claim 19, and claim 22 has been amended to refer to the subject matter previously presented in claim 21. Reconsideration is expressly requested.

Claims 17, 20, 21 and 22 were rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Stahl et al.*, 2002, International Journal of Pharmaceuticals, 233, 227-237. Claims 17 and 20-22 were rejected under et 35 U.S.C. 103(a) as being unpatentable over *Stahl et al.* in view of *Edwards et al. U.S. Patent Application Publication No. 2002/0052310*. Claims 17-22 were rejected under 35 U.S.C. 103(a) as being unpatentable over *Stahl et al.* and *Edwards et al.* and further in view of *Staniforth et al. U.S. Patent Application Publication No. 2003/0165436*.

In response, Applicants have amended claim 17 to better define the invention and respectfully traverse the Examiner's rejection for the following reasons.

As set forth in claim 17 as amended, Applicants' invention provides microparticles stable and storable at room temperature of insulin. The microparticles show a d90 volume diameter lower than 9 μm, and 80% of them exhibit an aerodynamic diameter lower

than 5 μm. The microparticles also have a corrugated or raisin-like surface and a moisture content in the range of 2 to 80%. As recited in claim 17 as amended, the microparticles are obtained by spray drying an aqueous solution of insulin having an acid pH under the isoelectric point (5.4) of insulin and a concentration of insulin in amounts of from 5 to 100 mg/ml. The aqueous solution is prepared in an unbuffered aqueous solution of acetic acid.

In this way, Applicants' invention provides microparticles of insulin stable and storable at room temperature and suitable for pulmonary administration for the long term treatment of diabetes in which the structure of the microparticles imparts an elevated respirability, together with favorable flow and packing characteristics.

The Examiner has taken the position at pages 3-4 of the Office Action that *Stahl et al.* "teaches that the insulin was dissolved in distilled water to obtain a solution with pH below the isoelectric point (pH 5.4) and the concentration of the solution held at 5 mg/ml (page 228, column 2, paragraph 2) that reads on the concentration limitations 5-100 mg/ml" as recited in

amended claim 17. Later on at page 4 fo the Office Action, the Examiner acknowledges as follows:

> "The reference does not explicitly [teach] that the aqueous solution of insulin be prepared in aqueous solution of acetic acid. Since the cited reference of Stahl, teaches the effect of process variables on the degradation and physical properties of spray drying of insulin, one of ordinary skill in the art would look at the effect of varying the pH of the spray drying solution on the stability of the microparticles of insulin. Hence where applicants claim a process of preparation of insulin by spray drying not explicitly taught by the cited reference of Stahl, a rejection under 35 USC 102(b)/103 is proper (MPEP 2113 [R-1)."

It is respectfully submitted that the Examiner's position is unfounded. The sole preparation method given in *Stahl et al.* can be found at page 228, first paragraph of section 2.2., where it is disclosed that

> "Insulin solutions were prepared by adding distilled water to insulin, reducing the pH below the isoelectrical point (pH 5.4) to fully dissolve the insulin. Thereafter the pH was increased to physiological pH i.e. 7.4. The feed concentration was held constant at 5 mg/ml throughout all the experiments."

Therefore, the solution pH is taught by *Stahl et al.* to be reduced below the isoelectrical point, without specifying how,

and then increased at physiological pH of 7.4 before spray drying. In other words, it is respectfully submitted that **the Examiner arbitrarily isolated a sentence part from *Stahl et al.*, thus decontextualizing the information in order to arrive at Applicants' invention as recited in claim 17, which it is respectfully submitted is a clear case of *hindsight* reconstruction of Applicants' invention** as recited in amended claim 17.

As a matter of fact, it is respectfully submitted that *Stahl et al.* is indeed focused only on the spray drying parameters, thus absolutely disregarding both the conditions of the solution preparation and the storage crucial aspects of the spray dried insulin so obtained.

Thus, it is respectfully submitted that a **skilled person** reading *Stahl et al.* **is aware only that the pH of insulin solution is reduced below the isolectrical point solely in order to fully dissolve the insulin, no matter how, and that the pH must be increased to a physiological pH of 7.4 before spray drying the solution.**

In contrast, as discussed in Applicants' disclosure at page 5, first full paragraph:

> "the spray drying of clear, concentrated, aqueous solutions of insulin having pH lower than the isoelectric point of the hormone (5.4), produces very high respirable dry powders. These powders can be obtained from unbuffered or volatile buffer solutions and were never prepared before. The spray drying of insulin solution under the isolectric point and therefore, in acidic conditions and without the use of permanent buffering agents, was not previously considered likely for stability and respirability reasons. On the contrary, insulin microparticles produced by spray drying acidic solutions of the hormone resulted in powders particularly suitable for lung administration, because they exhibit a high respirable dose. In addition, the stability was acceptable in refrigerated conditions but, **when the powder was manufactured from a solution in acetic acid (volatile buffer), the stability resulted surprisingly very high also in normal conditions.** Since no permanent buffers were used, it is also expected that these powders inhaled at the therapeutic doses do [not] modify the alveolar surfactant pH." (emphasis added)

Later on, at page 5, second full paragraph, Applicants' disclosure also states that:

> "The microparticles obtained according to the present patent are much more than dimpled since they are corrugated or raisin like FIGS. 1 and 2). In addition, they are **non-cohesive with favourable aerodynamic size and density characteristics.**" (emphasis added)

In the paragraph bridging pages 5-6 of Applicants' disclosure, it is further explained that:

> "when the volatile organic acetic acid is used to dissolve insulin, **powders obtained by spray drying from these low pH solutions have lost acidity**. In fact, the dissolution of these powders in distilled degassed water gives rise to a solution having pH higher than the value of the original solution. This fact made this powder **chemically very stable during storage.**" (emphasis added)

Again, at page 6, first full paragraph, it is stated that:

> "This particle shape makes the powders not cohesive since the **microparticles maintain their individuality and do not agglomerate**. In addition, they show substantially no losses of activity if stored in refrigerated conditions, but when they are prepared **from acetic acid**, the insulin powders are very **stable** also **at room conditions** (25°C). In particular, we surprisingly discover that the acetic acid solution of insulin at pH 3.3 after spray drying gave rise to a powder that re-dissolved in distilled degassed water at 1 mg/ml showed a pH of 6.4. Surprising this powder shows **a superior stability at 25°C, allowing the preparation to be used and dispensed at room conditions**, in comparison with insulin spray dried powders prepared with HCl that must be stored at refrigerated conditions." (emphasis added)

Finally, at page 6, last paragraph, and page 7, first paragraph, it is stated that:

> "The use of acidic solutions avoids the risk of precipitation induced by increasing the pH above insulin isolectric point up to neutrality, but more interestingly provides a structure to dried product that suprisingly is very useful for the aerosolization. In fact, these **powders** other than to be micronized, are **not cohesive, quite free flowing and easy meterable in the DPI**. These physical properties, together with the **favourable aerodynamic behaviour due to the size, shape and density of the particles,** determine **an unexpected and surprisingly high respirability**."
>
> "Finally, the powders contain residual moisture enough to prevent excessive degradation and they **can be stored at normal humidity and temperature conditions when prepared from volatile acetic acid.**" (emphasis added)

In this regard, it is respectfully submitted that claim 17, as amended, not only is new over *Stahl et al.* because a high number of features are not disclosed therein, but also **non-obvious** because *Stahl et al.* fails to disclose or suggest at all **the stability as well as the storage crucial aspects** as is done with Applicants' microparticles as recited in claim 17 as amended.

As a matter of fact, *Stahl et al.*, while teaching that the pH must be 7.4 before spray drying, actually **ignores the risk of precipitation** induced by increasing the pH above the insulin isoelectric point up to neutrality, as above indicated in page 6,

last paragraph quoted above, thus leaving absolutely unresolved the problem to which Applicants' invention as set forth in amended claim 17 is concerned.

This absence of teaching and failure to even recognize the problem becomes more evident when considering the statement of *Stahl et al.*, at page 234, end of section, that "The influence of the moisture content upon long term storage was outside the scope of this work. However, it should be mentioned that, in general, small particles within the inhalable size range may quickly adsorb moisture from air if they are hygroscopic and stick together in ways so that **they are not dispersed prior to inhalation**." (emphasis added)

Therefore, it is respectfully submitted that a person skilled in the art would have never found in *Stahl et al.* any suggestion or motivation that would lead one to Applicants' microparticles as recited in claim 17 as amended, which are stable and storable at room temperature, non-cohesive with favorable aerodynamic size, without the problem of undesired precipitation of insulin during the preparation and without requiring buffer solutions. For this reason, claim 17, as amended, is expressed as a **product-by-process** claim because the claimed combination of process features are configured to impart

to the microparticles the claimed product features that allow the achievement of the above explained surprising and unexpected stability, respirability and suitability for room storage, use and dispensing. As a matter of fact, **all of the cited unexpected results** for the microparticles **can be mostly ascribable to the selection of acetic acid**, which it is respectfully submitted makes the **product-by-process** claim format particularly apt.

The defects and deficiencies to the primary reference to *Stahl et al.* are nowhere remedied by the secondary reference to *Edwards et al.* According to the Examiner at page 5 of the Office Action, *Edwards et al.* provides the teaching that "particles of insulin can be prepared by spray drying wherein the insulin may be dissolved in aqueous buffer system such as acetate [0126]."

Edwards et al., however, concerns a "method for the pulmonary delivery of therapeutic, prophylactic and diagnostic agents comprising administering to the respiratory tract of a patient in need of treatment, prophylaxis or diagnosis an effective amount of particles comprising a therapeutic, prophylactic or diagnostic agent or any combination thereof in association with a charged lipid, wherein **the charged lipid has an overall net charge which is opposite to that of the agent**

[upon association with the agent]." (see paragraph [0030] of *Edwards et al.*) (emphasis added)

At paragraph [0124], *Edwards et al.* states that the particles can be fabricated or separated, for example, by filtration or centrifugation, to provide a particle sample with a preselected size distribution. Alternatively, at paragraph [0125] spray drying is proposed of a mixture including "the bioactive agent **and** one or more charged lipids having a charge opposite to that of the active agent upon association are fed to a spray drier." (emphasis added) Later on at paragraph [0126], relied on by the Examiner, *Edwards et al.* states that "In one preferred embodiment, the pH may be adjusted to about pH 7.4. At this pH insulin molecules have a net negative charge (pI=5.5). In another embodiment, the pH may be adjusted to about pH 4.0. At this pH insulin molecules have a net positive charge (pI=5.5). Typically the cationic phospholipid is dissolved in an organic solvent or combination of solvents. The two solutions are then mixed together and the resulting mixture is spray dried." (emphasis added)

Therefore, it is respectfully submitted that a person skilled in the art knows from *Edwards et al.* only that **irrespective of whether the pH is above or below the isolectrical**

point of the active ingredient, a **phospholipid having charge opposite** to that of the active ingredient **must** be mixed together, in the optional presence of a buffer system, and then spray dried.

Therefore, it is respectfully submitted that a person skilled in the art would not have contemplated combining *Stahl et al.* with *Edwards et al.* when *Edwards et al.* **clearly provides for features expressly excluded or in any event not even cited in Applicants' claim 17 as amended**, such as the **phospholipid having charge opposite** to that of the active ingredient, which is given as an essential feature in *Edwards et al.* (see claim 1 of *Edwards et al.*), and **optionally a buffer system** can be used, where the acetate is one of the possible buffers given by way of example (see paragraph [0126], second sentence of *Edwards et al.*) and when the sole example of *Edwards et al.* using buffer is at paragraph [0162], where the lipid is dissolved in ethanol and insulin, leucine and/or sodium citrate are dissolved in water.

Therefore, it is respectfully submitted that the Examiner is merely pointing to selected items in combination of references, where the secondary reference does not mention the feature of using acetic acid, in order to arrive at the supposed obviousness of Applicants' microparticles as recited in claim 17 as amended.

Thus, it is respectfully submitted that **the Examiner's conclusions are based on additional *hindsight***, because it is respectfully submitted that a person skilled in the art would have no reason to take *Edwards et al.* into consideration or even to combine *Edwards et al.* with *Stahl et al.* in order to achieve Applicants' invention as recited in claim 17, as amended, and the surprising and unexpected results that are achieved therefrom.

Even if *Stahl et al.* and *Edwards et al.* were hypothetically combined as suggested by the Examiner, however, it is respectfully submitted that the teachings of these two documents would at most lead a person skilled in the art to try the spray drying conditions as set forth in *Stahl et al.* to the active agent-phospholipid ionic complex disclosed in *Edwards et al.*, while **still disregarding**:

- all the **stability and storage crucial aspects** of insulin particles obtained,
- the use of **permanent buffering agents** implies for **stability and respirability problems** and can modify the alveolar surfactant pH (see page 5, first full pararaph of Applicants' disclosure) and
- **the risk of precipitation** induced by increasing the pH above insulin isoelectrical point up to neutrality, as

above indicated in page 6, last paragraph of Applicants' disclosure, thus leaving absolutely unsolved both the problems to which Applicants' invention as set forth in amended claim 17 is directed.

The remaining reference to *Staniforth et al.* has been considered but is believed to be no more relevant. *Staniforth et al.* discloses formulations for use in an inhaler device, comprising carrier particles having a diameter of at least 50 μm and a mass median diameter of at least 175 μm; fine particles of an excipient material having a mass median aerodynamic diameter of not more than 20 μm; and active particles.

The Examiner considers *Staniforth et al.* relevant because among all of the possible acceptable pharmacologically inert carriers, mannitol is cited by way of example at paragraph [0017] of *Staniforth et al.*, whereas, analogously, insulin is cited among all the possible therapeutically active ingredients (see paragraph [0037] of *Staniforth et al.* The Examiner states at page 6 of the Office Action that the tapped density indicated at paragraph [0024] of *Staniforth et al.* being not more that 0.7 g/cc "reads on the particle size limitation of the instant application and hence reads on" claim 18.

It is respectfully submitted that even if the Examiner's position is correct, the Examiner nonetheless **arbitrarily decontextualized the above information**, while **forcing them to match the microparticles features of Applicants' invention as recited in claim 17 as amended** in a further *hindsight* reconstruction of the invention.

This hindsight reconstruction becomes even more evident when considering that the Examiner has apparently overlooked that the above cited **tapped density** is not referring to microparticles of active agent, or accordingly to insulin, but instead is **referring to the carrier particles having fissured surface**. The tapped density of the fissured carrier particles is well disclosed in paragraph [0024] of *Staniforth et al.*, where the above value, i.e. not more than 0.7 g/cc, is expressly related to the sole lactose.

Thus, it is respectfully submitted that the teaching of *Staniforth et al.* as a whole is definitely different from **the sole part pointed to by the Examiner**. Even in this case, it is respectfully submitted that a person skilled in the art would have no reason to contemplate combining *Stahl et al.* with *Edwards et al.* and *Staniforth et al.* when *Staniforth et al.* **clearly does not pertain to the field of endeavor of Applicants' invention as**

recited in claim 17 as amended, besides requiring that person to disregard all the aspects listed above for *Edwards et al.*, and additionally in *Staniforth et al.* the spray drying is never cited for producing the particles.

In this regard, it is respectfully submitted that **a suggestion or motivation to combine *Stahl et al.* and *Edwards et al.* with *Staniforth et al.* can nowhere be considered present when both the previous teachings as discussed above, either alone or taken together, relate to spray dried particles.** Furthermore, **it is respectfully submitted that a person skilled in the art would not have been motivated to consider the tapped density of lactose, as carrier in non spray dried formulations, suitable for the spray dried microparticles of insulin in order to achieve long term stability and storage at room temperature of the microparticles themselves.**

In view of the foregoing, it is respectfully submitted that **the Examiner's rejection is based on *hindsight* derived from knowledge of Applicants' invention as recited in claim 17 as amended**, where it is clear that a person skilled in the art would have no reason to take *Staniforth et al.* into consideration let alone combine the same with *Stahl et al.* and/or *Edwards et al.* in

order to achieve Applicants' invention as recited in claim 17 as amended.

Accordingly, it is respectfully submitted that claim 17 as amended, together with claims 18-22, which depend directly or indirectly thereon, are patentable over the cited references.

In summary, claims 17, 19, and 21-22 have been amended. In view of the foregoing, it is respectfully requested that the claims be allowed and that this case be passed to issue.

Respectfully submitted,

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